Biological Product Inspection Issues and Regulatory Update

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Items to be covered....

- Overview of inspection programs
- Review process and inspections
- Potential problem areas – focus on pre-license/pre-approval inspections (PLI/PAI)
- Issues found during the review and inspection that can delay approval
- Regulatory update - Staying ahead of the curve

Definition – Pre-license (PLI)

- Subject to Biologics License Application (BLA)
- May be non-U.S. licensed firm
- May be U.S. licensed firm with a new product
- May involve several sites
- Necessary for licensure under 21 CFR 601.20(d)

Definition – Pre-approval (PAI)

- Product under NDA, ANDA, NADA or PMA review
- Subject to a Prior Approval Supplement under the regulations

  - for new manufacturing facility

  - for a contract facility

  - when there have been significant process changes

FDA Inspections for Biologics Products - Who Does What?

- Depending on the type of inspection: CBER, Team Biologics, or District Office may conduct the inspection
- Products regulated by CBER - CBER will conduct the PLI/PAIs; Team Biologics will conduct routine GMP inspections
- Team Biologics - performs routine GMP inspections for biologics products (CBER and CDER), product specialists participate

FDA Inspections for Biologics Products - Who Does What?

- FDA District Offices (field) - performs routine GMP inspections for other pharmaceutical products and Pre-approval inspections (PAIs) for traditional pharmaceuticals. Field is invited and may participate in PLA/PAIs for CBER-led inspections.

Inspection Focus and Impact

- GMPs evolve, and the focus of inspections may change in response to problem areas or for new initiatives
- Consequences of problems encountered during review and inspection - multiple rounds of submissions and delayed approval
- Consequences of routine GMP inspections - It is uncommon that a single “catastrophic” issue will lead to compliance action(s); more common to take compliance actions when there is a pattern of violations or repeated violations

Focus of the Inspection

- Routine GMP inspection - quality systems, adherence to GMPs, follow-up from previous inspections
- PLI/PAIs cover GMPs, but also need to verify information submitted for review
- Not surprisingly, the issues found on an inspection are influenced by a number of factors, all other things being equal

Looking for Inspectional trends?...It will Depend...!

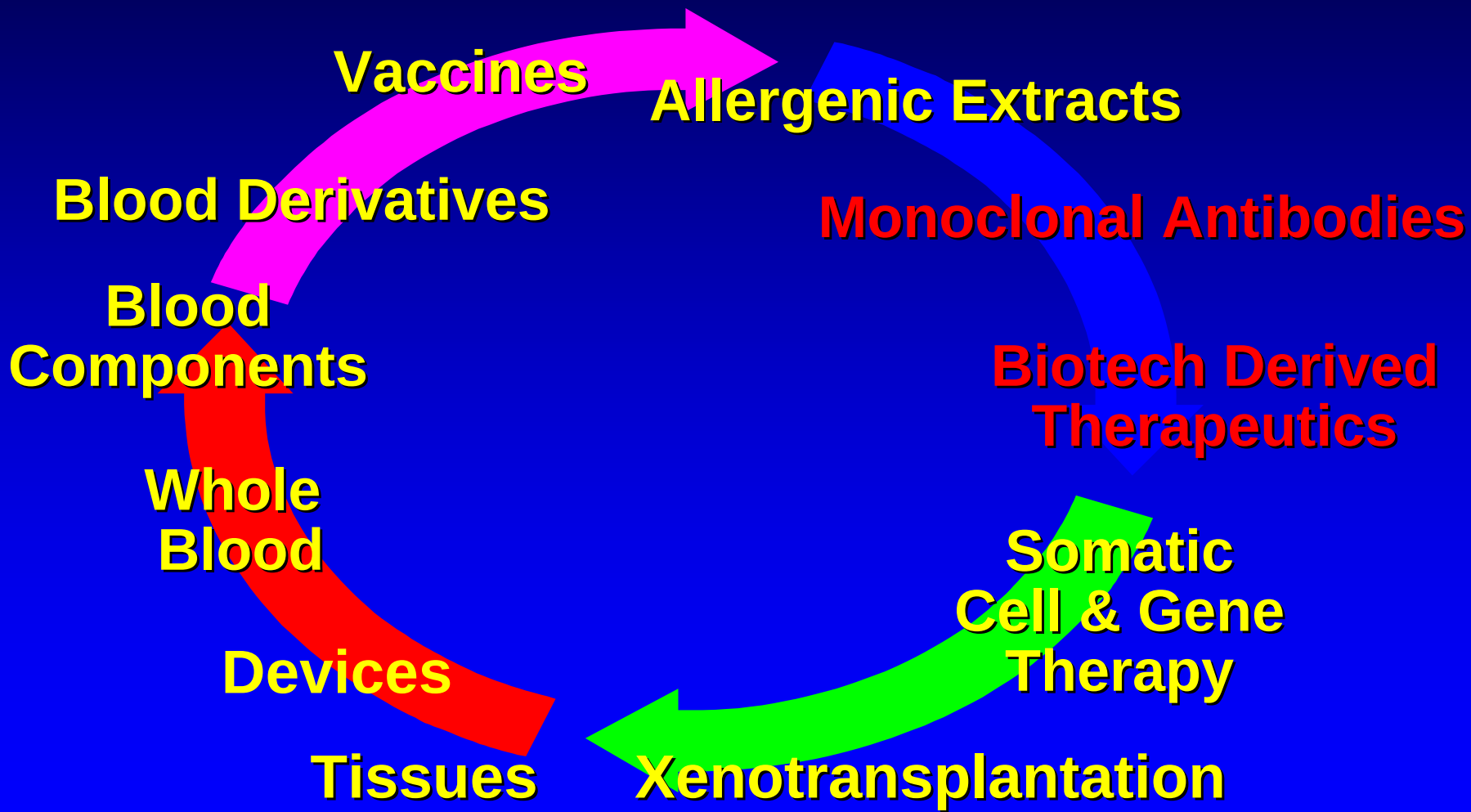
- Factors that influence the issues found:
- PLI/PAI vs routine GMP inspection
- Experience and history of firms
- Going from R&D to license/market approval
- Older facilities
- Contract manufacturing - seems to cut across all experience levels

One recent look at inspections found….*

- For field routine GMP inspections, failure to follow procedures was most common citation.
- For field PAIs, laboratory issues were most often cited.

*the Gold Sheet, May 2004

Now to Focus on Biological Products



CBER Reviews and Inspections

- Pre-license/pre-approval inspections are an integral part of application/supplement review process prior to approval
- Pre-approval inspections are conducted by CBER (review committee)
- CBER reviewers provide recommendation for approval of application/supplement

Review vs Inspection

- Remember that there is limited facility/GMP information in biologics product submissions
- Issues not in CMC or supporting guides become inspection issues
- Many of the issues can only be determined during the inspection (SOPs, EM, deviations, investigations, records)
- CBER PLIs/PAIs comes midway through the process and are preannounced

A Summary of Review Issues

- Validation issues - validation incomplete; scale-up issues not addressed
- Insufficient information or RTF issues such as lack of complete sections (aseptic processing)
- Product comparability from multiple sites
- Stability issues

Firms going from R&D to marketing often....

- Have incomplete quality systems and procedures
- Incomplete documentation (batch records, environmental monitoring)
- Have not completed all equipment qualification or process validation

More experienced firms have issues with...

- Following existing systems, such as failure investigations, completion of deviations, taking appropriate corrective actions
- Verifying that process changes, either single or cumulative, have not had adverse effects on product quality


A QUALITY PRODUCT
QA/QC
VALIDATION/QUALIFICATION
ROUTINE MONITORING
EQUIPMENT
PROCESS
COMPONENTS
ENVIRONMENT
RAW MATERIALS

Issues to Consider for Facilities and Operation

- Are support systems (HVAC, WFI) adequate?
- Is the design adequate for expansion, facility changes, retrofitting?
- Proper segregation of process steps?
- Multi-product/multi-host issues addressed?
- Contract manufacturing(adequate control?)
- Quality systems in place?

General Issues to Consider for Facilities

- Older facilities
  - Suitable for the new product/process?
  - Retrofits and system capabilities
- New facility
  - Designed for R&D but not GMP
  - Adequate control through procedures and personnel
  - Occasional pilot batches vs continuous production

Multi-Product Issues

- Campaign vs concurrent production will impact on design and operation of the facility
- Commercial vs investigation product manufacturing
- Dedicated vs shared equipment
- Multiple host cells

Problem areas: Facility Issues

- Improper qualification of facilities
- Equipment qualification/suitability issues
- Contamination in equipment that is difficult to eradicate
- Introduction of new products - cleaning validation and product changeover issues

Problem Areas: Operation/Quality Issues

- Product comparability between facilities or suites, or duplicative process trains
- In-process bioburden specifications not set or followed
- Column life span not fully validated
- Laboratory issues (assay validation, OOS)
- Quality oversight issues

Inspection Issues and Observations: Examples

- Facility and production environment
- Process related issues
- Quality Unit related issues

Facility issues - design and control

- Are there adequate areas to perform manufacturing steps and do they appear under control? (Appropriate room classification, evaluation of surfaces, drains, are there excursions in environmental monitoring, HEPA certification)

Facility - HVAC Monitoring

- Are the controlled production environments appropriately monitored for HVAC system performance and microbiological quality?
- Pressure differentials, appropriate sampling sites under appropriate conditions, adequate sampling frequency

Facility-Related Issues FDA 483 Example

- "Alarm excursions for pressure and particles in aseptic filling suite and associated … rooms were not documented…. Multiple instances for over 14 minutes during…production" "Non conformance reports were not initiated…nor were they noted in the batch record…"

Facility - Water Monitoring

- Is the water system appropriately monitored for system performance? (sampling sites, sampling frequency)
- FDA 483 example “Sampling of <water system> does not reflect actual use in production. For example, prior to sampling, there is a 3 minute flush and production does not include a flush prior to use.”

Facility Issues - Support Systems and Equipment

- Are the clean steam and compressed gas systems appropriately monitored?
- Equipment qualified for intended use?
- Product contact surfaces appropriately addressed? (cleaning, sterilization, changeover, storage)
- Performance testing performed? (filter integrity testing)

Facility issues - Personnel

- Personnel gowning practices appropriate? (includes segregation of steps)
- Personnel adequately trained?
- Supervisors experienced with the process?
- Quality approach to operations?

Personnel-related 483 item

- “Operators qualified to work in the aseptic processing suite had skin exposed <face> under laminar airflow in the Class A area while performing aseptic operations <6 different items were noted>”

Process Issues

- Conformance lots produced using the method submitted in the license?
- Can lots be manufactured consistently? (process validation or equipment suitability issues)
- Hold steps/storage/shipping validated (product stability, container/closure, max hold times, bioburden limits).

Process Issues: Validation FDA 483 example

- “Process validation to support manufacture was incomplete <including> dissolution, filtration, and other process parameters.”

Process Issues: Process control FDA 483 example

- "Since June 2002, 6 of 10 bioreactors have become contaminated and terminated, affecting X lots. In addition, the media in two other bioreactors was found to be contaminated, prior to inoculation…" "The possible causes have varied…not all corrective actions were implemented prior to initiating other bioreactor runs."

Process Issues: FDA 483 example

- “The holding time for sublots prior to their use in final bulk product has not been validated.”
- “Validation data were not available for the <X> month in-process hold time for <drug substance>”

Process Related Issues

- Are in-process specifications supported by data? (bioburden, protein, activity, etc)
- If reprocessing or rework steps have been used, are they validated or ongoing validation?
- Routine use of purification columns controlled? (resin lifetime, sanitization and storage)

Process Issues: Bioburden FDA 483 Example

- "The ultrafiltration step after cell culture harvest is not validated with respect to bioburden control." During validation, lot XXX was OOS for bioburden at the UF/DF step."
- Bioburden in the UF/DF pre-filtration pools were implicated as the cause of OOS XXX levels in several lots.

Process Related Issues

- Are qualifications for critical equipment performed appropriately?
- Do SOPs reflect the qualified conditions for use of the equipment?
- Adequate cleaning validation?
- And there are many more!!!!

Quality Unit Issues

- Appropriate oversight: Adequate review and approval of records, procedures, and final release of product?
- Are deviations reported and investigations performed? (OOS results, revalidation, investigations complete)
- Change control procedures for SOPs in place?

Quality Unit Issues
FDA 483 Examples

- "The product release procedure does not include documentation demonstrating that the QA/QC director reviews the EM data and deviation reports prior to product release."
- "There is no SOP for the release of formulated purified bulk to the contract filler."

Quality Unit Issues
FDA 483 Example

- "Quality unit does not maintain control of master versions of Standard Operating Procedures."

Quality Unit Issues - Testing

- Method validations submitted in the application supported by the raw data?
- Are in-process and final testing samples being handled appropriately?
- Is testing equipment being appropriately maintained and are there records?

Multiple Use and Contract Manufacturing Facilities

- Know in advance the products that will be produced
- Know the full range of adventitious agents possible
- Have adequate change control
- Contracts: Make sure that responsibilities of all parties are adequately addressed
- Contracts: Make sure that changes will be reported

Contract Manufacturing

- Most contract facilities will be multi-product facilities
- How well will applicants oversee their contract facilities?
- How will applicants be able to assess the impact of other products in the facility?
- When will applicants know of important changes in their contract facilities?
- Assessment of compliance history of contractor?

Principles for Contract Manufacturing

- Regardless of the party performing a manufacturing step, adequate control over manufacturing is maintained
- Ultimately the applicant is responsible for all manufacturing, testing, and quality aspects of the product
- There should be lot-to-lot consistency of the product though a controlled process, regardless of the site of manufacture

What you don’t want to happen during the Inspection

Who is responsible???

Applicant

Contractor

FDA

Problem areas in contract manufacturing (from reviews and inspections)

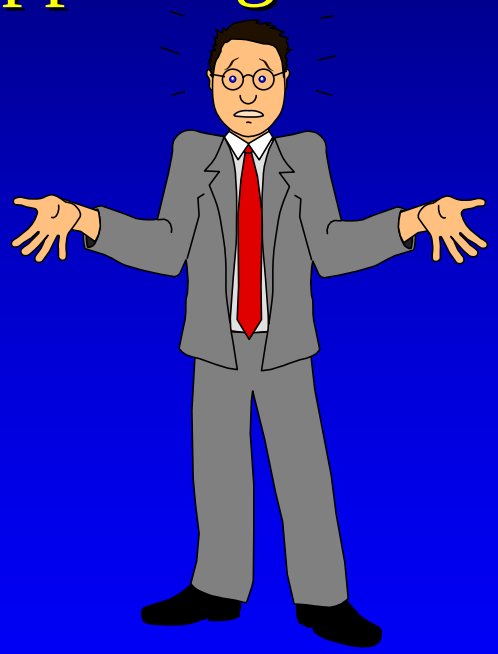
- Clearly defining the responsibilities of all parties
- Oversight of contract facilities by applicant
- Coordination of information submitted in application and supporting submissions
- Transport of product between facilities
- GMP compliance of the contract facility

Keeping up with the Changes

- Keep up with the latest inspection trends*
- Keep up with the latest regulatory initiatives
- Have meetings with FDA at critical points during the process or when major changes are anticipated

Moving forward...

- What is happening at FDA?



Selected Regulatory Initiatives…

- CGMPs for the 21st Century
- Critical Path
- Efficient Risk Management
- Selected Guidance Documents

CGMPs for the 21st Century - A Risk-Based Approach

- Facilitate modern quality management techniques, including quality system approaches, to production and QA
- Encourage new advances in technology and implementation of risk-based approach
- Ensure regulatory review and inspection policies are based on current science
- Enhance consistency and coordination within the Agency

CGMPs for the 21st Century - A Risk-Based Approach

- CBER previously adopted the use of product specialists on inspections, specialized teams and training, risk-based prioritization, Center review of Warning Letters
- Additional Center Initiative: Enhance inspectional and compliance integration/coordination with product review process

Final Report

- Issued September 29, 2004
- Key accomplishments:
  - Quality Systems model for Agency operations
  - Quality Systems guidance for CGMP regulation
  - Adoption of risk management principles
  - Risk-based pharmaceutical quality assessment system
  - Development of science-based policies

http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm

CGMPs for the 21st Century - A Risk-Based Approach

- Sterile Drug Products Produced by Aseptic Processing (9/2004)
- Comparability Protocols for Protein Drug Products and Biological Products (9/2003)
- Quality Systems Guidance Document (9/2004)
- Systems-based Compliance Program for Biological Drugs (12/2004)
- Good Review Management Principles and Practices for PDUFA products (4/2005)

Critical Path Initiative

- Facilitate product development through better tools and latest technologies for product manufacturing, and for ensuring safety and efficacy
- Target unmet needs with regulatory implications to facilitate development of products - as resources permit
- Identify the gaps, scientific and regulatory, and develop appropriate solutions

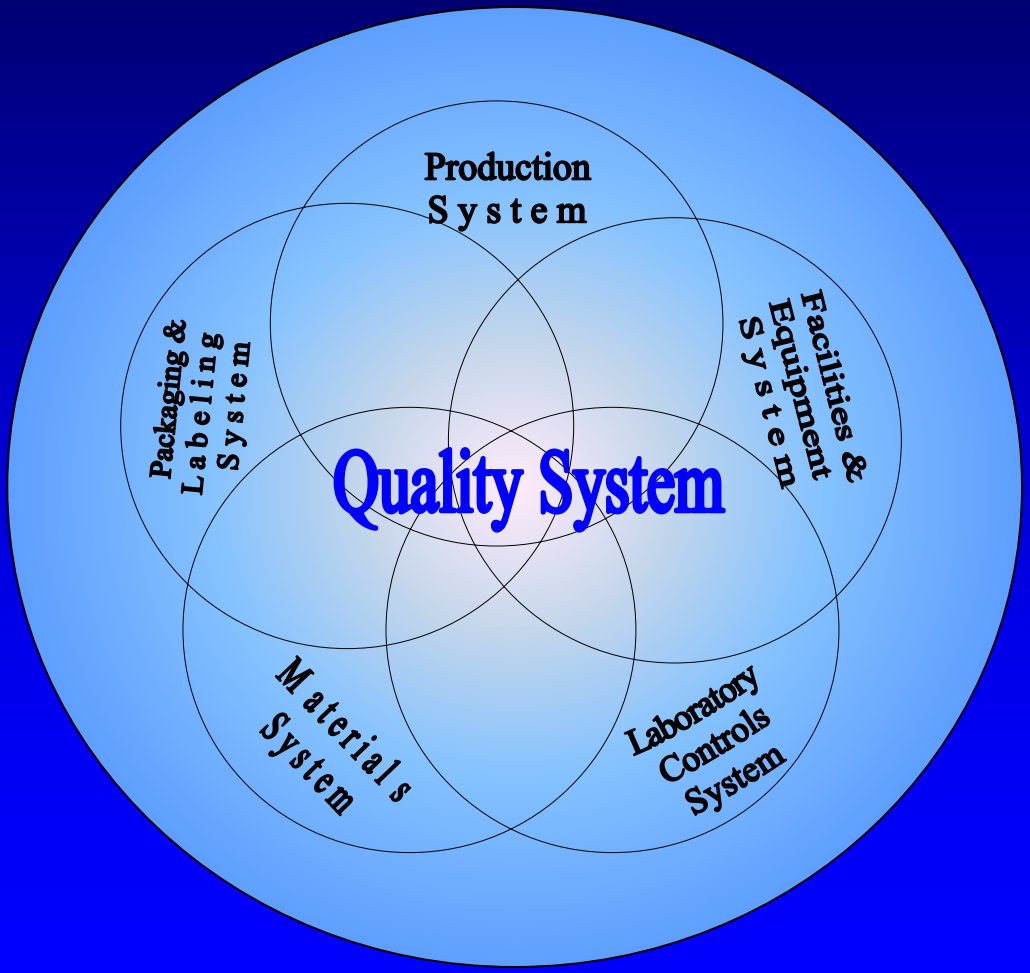
Critical Path Initiative

- Maintain staff “cutting edge” expertise needed for addressing issues of evolving biotechnologies
- Having science drive the regulatory process, less “defensive” and reduces the risks of over or under protectiveness

Efficient Risk Management

- Enhanced Review Process Management and Processes
  - Identify best practices
  - Review template initiative to enhance the consistency and quality of the reviews
  - Monthly meetings for CBER staff to discuss regulatory issues

Systems-based approach



Summary Potential Approval Delay Issues

- Process Validation
- Manufacturing consistency
- Equipment and Systems Qualification
- Quality Oversight
- Standard Operating Procedures

Summary

- Discussed issues found during inspections with emphasis on problem areas and trends
- Discussed several observations to focus attention on problem issues
- Discussed several (but not all!) Agency initiatives to further facilitate product development
- Good communication with FDA and keeping current will minimize problems!

For more information….

- CBER/FDA web site: www.fda.gov/cber/ contains
  - guidance documents
  - presentations
  - FR notices
  - compliance policy references
- Technical issues: webmaster@cber.fda.gov
- Manufacturers assistance: matt@cber.fda.gov
- eltermann@cber.fda.gov

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